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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,117	11/06/2000	Jon A. Wolff	Mirus.018.02	8189

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/707,117	Wolff et al.
Examiner	**Art Unit**
Michael C. Wilson	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *2-5-02 and 9-26-02*.

2a) [X] This action is **FINAL**. 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-3, 5-7, 11, 12, 16-20, 24, 25, 27-31, 34-36, and 38-42* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-3, 5-7, 11, 12, 16-20, 24, 25, 27-31, 34-36, and 38-42* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [X] Other: *def. of "immunosuppression"*

DETAILED ACTION

A non-responsive letter was sent 9-26-02, paper number 8, was sent because support for claim amendments made 7-12-02 had not been provided. The response filed 1-3-03, paper number 9, provided support for the claim amendments. Applicant's arguments filed 7-12-02, paper number 7, have been fully considered but they are not persuasive. Claims 4, 8-10, 13-15, 21-23,26, 32, 33 and 37 have been canceled. Claims 1-3, 5-7, 11, 12, 16-20, 24, 25, 27-31, 34-36 and 38-42 remain pending and under consideration. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

1. Claims 1-3, 5-7, 11, 12, 16-20, 24, 25, 27-31, 34-36 and 38-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation of applying pressure to the limb epidermis (claim 1 and 39) is not the same scope as applying a cuff or sphygmomanometer to the skin around a limb (pg 5, line 21). The epidermis is a layer of skin and is a narrower scope than originally contemplated in the specification. Nor does the specification contemplate merely applying pressure to the skin as broadly claimed. The specification only contemplates applying a cuff, e.g. a sphygmomanometer, to the skin (pg 5, lines 13-24).

The limitation of "continuous" and "transient" "immunosuppression" (claim 1) does not have support on pg 3, line 26, which only contemplates "immunosuppression can be long term and for a short duration." Immunosuppression is obtained by treatment with drugs. The specification does not contemplate "applying" immunosuppression as newly claimed. The specification does not contemplate delivering drugs "continuously" or "transiently"or define the metes and bounds as they relate to "long term" and "a short duration" as originally disclosed. As such, the step is new matter.

The limitation of "function is not affected by the delivery process" does not have support in the specification as originally filed. Applicants have not provided support for the amendment and none can be found.

2. Claims 1-3, 5-7, 11, 12, 16-20, 24, 25, 27-31, 34-36 and 38-42 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a marker protein operably linked to a promoter and wherein said marker protein is expressed to detectable levels in muscle cells of said limb, does not reasonably provide enablement for the methods claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claim 39 encompasses injecting any blood vessel with any polynucleotide, using any method of immunosuppression and any method of impeding blood flow such that polynucleotide is delivered to a skeletal muscle cell. Claim 1 requires delivery to a skeletal muscle cell. Claim 5 requires delivery to a skeletal muscle cell. Claims 6-31 require delivery to skeletal muscle cells of limbs, some of which require delivery to specific muscles within the limbs. The purpose of delivering DNA to skeletal muscle cells is to express DNA in skeletal muscle cells.

Vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art (Miller of record, 1995, FASEB J., Vol. 9, pages 190-199; Deonarain of record, 1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69; pg 53, first paragraph; pg 65, first para. under Conclusion section; Verma of record, Sept. 1997, Nature, Vol. 389, pages 239-242; see entire article; pg 240, sentence bridging col. 2 and 3; Crystal of record, 1995, Science, Vol. 270, pg 404-410; pg 409).

The specification teaches administering naked plasmid DNA encoding a marker protein operably linked to a promoter to an artery of the arm or leg and obtaining expression in muscle cells of the arm or leg, respectively. However, Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203) taught administering adenoviral particles to a femoral artery and vein occluded using a tourniquet. The adenoviral vector encoded LacZ which was expressed in hepatocytes but not in muscle cells of the limb (page 2201, col. 2, 2nd para.). Ye (March 1, 2000, Human Gene Therapy, Vol. 11, pg 621-627) taught administering adenoviral particles encoding LacZ to the portal vein/artery occluded with clamps and obtaining expression in kidney, liver and spleen but

not in skeletal muscle or heart. The specification does not teach how to use adenoviral vector to obtain expression in skeletal muscle. The specification does not teach how to deliver DNA into the portal vein/artery and obtain expression in skeletal muscle. The specification does not teach delivering DNA to a non-leg or non-arm blood vessel and expressing the DNA in leg or arm skeletal muscle. For example, the specification does not teach delivering DNA to a blood vessel in the leg and obtaining expression in muscle cells of the arm. Given the unpredictability in the art taken with the lack of guidance provided in the specification, it would have required one of skill in the art at the time the invention was made undue experimentation to determine the parameters required to deliver DNA to skeletal muscle as claimed, particular to express the DNA in skeletal muscle.

Because of the lack of clarity regarding "externally impeding *in vivo* blood flow," "applying immunosuppression," the methods of delivery in claims 1, 3-35, 37-41 encompass the method of delivery taught Milas and the methods of delivery in claims 1, 3-32 and 37-41 encompass the method of delivery taught by Ye. However, the method of delivery taught by Milas or Ye cannot result in delivery to muscle cells of the limb as in claims 6-31. Therefore, claims 6-31 should not encompass methods of delivery taught by Milas and Ye.

The broad claims encompass any skeletal muscle and narrower embodiments require delivery to specific muscles of the arm and leg (claims 11, 12, 16, 17, 24, 25, 29-31). It cannot be determined how the delivery of DNA to specific muscles of the arm and leg is effected by the location of the blood vessel injected, the type of polynucleotide (adenovirus vs. naked plasmid

DNA), the method of occlusion (tourniquet vs. clamps, balloon catheter), or the method of immunosuppressing (administering vs. not administering an immunosuppressive agent) as broadly claimed. Applicants have not taught how much pressure is required to obtain expression in the specific skeletal muscles of the arm and leg. While the specification teaches expressing proteins in specific muscles of the arm and leg using naked plasmid DNA, the claims are not limited to naked plasmid DNA, and the specification does not correlate the results obtained with naked plasmid DNA to any other vector (e.g. adenovirus).

The specification does not provide adequate guidance for one of skill to determine why or when an immunosuppressive agent is administered, how administering such an agent effects the delivery of DNA or whether different immunosuppressive agents have different effects on the delivery of DNA. Nor can it be determined why one of skill would want to perform the method in an immunosuppressed mammal (SCID mouse, nude mouse, HIV infected human, etc.; see 112/2nd) which is also encompassed by the claims. Clarification is required.

The specification does not enable delivering any polynucleotide as broadly claimed. The specification only teaches delivering DNA encoding a marker protein operably linked to a promoter. The specification does not enable delivering any other polynucleotide or delivering DNA encoding a marker protein in the absence of a promoter. The specification does not enable one of skill to determine "blocking polynuceotides for preventing gene expression."

Applicants argue the amendments address the rejection. Applicants argument is not persuasive.

3. The rejections below are new, in part, based on the amendments to the claims.

Claims 1-3, 5-7, 11, 12, 16-20, 24, 25, 27-31, 34-36 and 38-42 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claims 1 and 39 are indefinite for the following reasons:

The limitations in d) (claim 1) or c) (claim 39) are unclear because they may be a result of the previous steps or may be a new step in addition to the previous steps. Clarification is required.

Step b) is unclear because it is unclear if "impeding blood flow" is required in the step or if it is merely an intended use when applying pressure to the mammal's epidermis.

Step c) is unclear because the metes and bounds of immunosuppression selected from the group consisting of "continuous and transient" is unclear. Immunosuppression is the suppression of the immune system as by a drug (see definition provided). Immunosuppression is not a drug and is not "applied" as claimed. "Continuous" and "transient" are not types of immunosuppressions. They are adjectives describing how the drug that causes immunosuppression is delivered. However, the metes and bounds of when a drug is delivered "continuously" or "transiently" is relative and not defined in the specification or the art at the time of filing. Overall, the use of "continuous" and "transient" to describe "immunosuppression" or how "immunosuppression" is "applied" is incorrect.

Claims 1 and 39 do not recite all the steps of the method because the mere delivery of polynucleotides to any cell does not have a disclosed use after delivering the DNA to a skeletal muscle cell. The method should result in expression of a protein in skeletal muscle cell.

Claim 5, 6, 18, 19, 20, 24, 27, 28, 30 is indefinite. A skeletal muscle cell does not consist of a limb muscle cell (claim 5) and because "skeletal muscle cell" is a different scope than "muscle cell". A skeletal muscle cell may be found in a limb or may be a limb skeletal muscle cell, but it does not consist of a limb skeletal muscle cell as claimed. Claims 6, 18, 19, 20, 24, 27, 28, 30 are indefinite for the same reasons.

Claim 11, 12, 16, 17, 34 and 35 are indefinite because they are dependent upon a claim that has been canceled.

Claims 11, 12, 16, 17, 30, 31 are indefinite because the species in the Markush group are types of muscles, not muscle cells as claimed.

The metes and bounds of what applicants consider an "internal" muscle cell cannot be determined (claim 27, 30) for reasons of record. All muscles are "internal" as they are not on the outside of the skin. Thus, the metes and bounds of "internal" muscle cells cannot be determined.

The notation "spf." and "prof." is unclear because it cannot be determined what the abbreviations mean (claims 11 and 12).

The metes and bounds of what applicants consider "compressing" skin cannot be determined (34-36). Is pinching the skin encompassed by the claim? If the polynucleotide is injected in the arm, does the claim encompass "compressing" the skin of the foot? There should

be a nexus between impeding blood flow of a blood vessel and applying pressure to that blood vessel by "compressing" skin. Similarly, there should be a nexus between impeding blood flow of a blood vessel and applying pressure to that blood vessel using a tourniquet, cuff or sphygmomanometer.

Claims 34-36 remain indefinite because a tourniquet or cuff is not "applied" "over the skin". A tourniquet or cuff is placed on an arm, leg, etc. Pressure may be applied to a blood vessel using a tourniquet or cuff.

The metes and bounds of "cuff" (claims 35, 36) cannot be determined. The term does not have a defined meaning in the art. The specification defines "cuff" as a devise for impeding blood flow in a blood vessel (page 5, line 13). While a sphygmomanometer cuff can be envisioned, and the specification states tourniquets are "cuffs," other cuffs cannot be envisioned. Thus, the metes and bounds of devises encompassed by the term "cuff" cannot be determined. Does the cuff have to be applied to the outside of the mammal or is a string around the blood vessel a cuff? The definition provided in the specification is confusing. Is a cuff a "device for impeding blood flow through mammalian internal blood vessels" (line 13) or a "device applied to exterior to the mammal's skin and touches the skin in a non-invasive manner" (line 14)? It cannot be determined which definition is to be applied. Therefore, the metes and bounds of the term cannot be determined.

The metes and bounds of "primarily" (claim 37) cannot be determined. Does the term mean greater than 50% or does it mean the greatest percentage? Deletion of the term is recommended.

The metes and bounds of non-vascular parenchymal cells cannot be determined. The specification and the art do not define the parenchymal cells of vascular tissue; therefore, the metes and bounds of non-vascular parenchymal cells cannot be determined. What are the distinguishing cells of a blood vessel as implied on page 10, line 1?

Claim 39 is indefinite because the metes and bounds of "full function" of a limb cannot be determined. Is full function limited to motor function, blood vessel function or neurological function or is it limited to the function of the limb itself? Is full function a relative term used to compare the function of a limb before and after treatment. Full function could encompass a limb having motor function, blood vessel function and neurological function after treatment, wherein the motor skills are impaired. Clarification is required.

Claim 39 is indefinite because the metes and bounds of "wherein function is not affected by the delivery process" cannot be envisioned. In addition, "the delivery process" lacks antecedent basis.

Claim 40 is indefinite because the metes and bounds of "continuous" treatment is unclear. Does the term mean the treatment is constantly going into the mammal or the treatment is given on a regular basis for a period of time? If it is given on a regular basis for a period of time, how

long is it given? Is treatment once a day for 5 days "continuous"? Is treatment once a day for the lifetime of mammal continuous?

Claim 41 is indefinite because the metes and bounds of the term transient treatment cannot be determined. How long is the treatment given? How long is the treatment not given? Is treatment once a day "transient" if the treatment maintains immunosuppression?

The relationship of the term "immunosuppression" with the Markush group of claim 42 is not correct. Immunosuppression is the suppression of the immune system as by a drug (see definition provided). Immunosuppression is not a drug and is not delivered as claimed. "Oral treatment" and "subcutaneous injection" are routes of administering a drug and do not apply to suppression of the immune system. However, immunosuppression may be obtained by delivering a drug orally or subcutaneously.

Applicants have not argued the indefiniteness rejections that have been maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claims 1, 3, 5, 6, 11, 12, 16, 17, 24, 25, 27-31, 34-36 and 38-42 remain rejected under 35 U.S.C. 102(b) as being anticipated by Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203).

Milas taught administering adenoviral particles to an occluded femoral artery and vein of a rat. The femoral artery and vein were occluded using a tourniquet applied to the skin of the leg (pg 2198, Fig. 1A, see tourniquet on rat). The adenoviral vector encoded LacZ which was expressed in hepatocytes; hepatocytes are parenchymal cells. The limitation of applying "transient" immunosuppression (step c; claim 41) is equivalent to temporarily occluding the blood vessels; the process of occluding blood vessels is "immunosuppression" because blood cells are prevented from flowing through that area. The limitation of applying "continuous" immunosuppression (claim 1, step c; claim 40) is taught by Milas because occlusion continues throughout the operation. The metes and bounds of "continuous" and "transient" immunosuppression are unclear (see 112/2nd). The DNA of Milas was inherently delivered to

skeletal muscle cells as claimed because occlusion of the femoral artery using a tourniquet results in delivery of the DNA to skeletal muscle (Example 10, pg 32). Milas taught LacZ was expressed in tumor cells which is equivalent to "expression at detectable levels" as claimed. (The claims do not require expression in skeletal muscle cells). Claim 42 is included because it is indefinite.

Applicants argue Milas did not teach applying pressure to the limb epidermis as claimed. Applicants arguement is not persuasive because Fig. 1A clearly shows applying a tourniquet to the leg which is equivalent to "applying pressure to the limb epidermis" as claimed.

5. The rejection below is new based on the amendments to the claims.

Claims 1-42 are rejected under 35 U.S.C. 102(a) as being anticipated by Von der Leyen (9-20-99, Human Gene Therapy, Vol. 10, pg 2355-2364).

Von der Leyen taught administering naked plasmid DNA into the carotid artery while applying a sphygmomanometer to the epidermis of the limb to increase the pressure of the artery to 300 mmHg (pg 2356 col. 2, "Transfection procedure"; pg 2360, Fig. 2, see 300). While Von der Leyen did not teach obtaining delivery to skeletal muscle as claimed, Von der Leyen taught obtaining expression in the layers of the carotid artery. The method of Von der Leyen inherently results in delivery to skeletal muscle as claimed because the carotid artery is surrounded by skeletal muscle, because the method of Von der Leyen forces the DNA through the blood vessel wall (pg 2362, col. 1, line 14), and because the method of administering taught by Von der Leyen is equivalent to the method claimed.

The rejection of claims 1, 3-32 and 37-41 under 35 U.S.C. 102(b) as being anticipated by Sferra (April 10, 1997, Human Gene Therapy, Vol. 8, pages 681-687) has been withdrawn because Sferra did not teach applying pressure to the mammal's limb epidermis as newly amended.

The rejection of claims 1-5, 8-10, 13-15, 32, 38-40 under 35 U.S.C. 102(e) as being anticipated by Wolff (US Patent 5,693,622 Dec. 2, 1997) has been withdrawn because Wolff did not teach applying pressure to the mammal's limb epidermis as newly amended.

The rejection of claims 1-32 and 37-41 under 35 U.S.C. 102(e) as being anticipated by Nabel (U.S. Patent, 5,910,488 filed 1-1-95) has been withdrawn because Nabel did not teach applying pressure to the mammal's limb epidermis as newly amended.

The rejection of claim 1-32 and 37-42 under 35 U.S.C. 102(b) as being anticipated by Nabel (U.S. Patent, 5,698,531, filed 1-23-95) has been withdrawn because Nabel did not teach applying pressure to the mammal's limb epidermis as newly amended.

Claim Rejections - 35 USC § 103

The obviousness rejections below are new based on the amendments to the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

> to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-3, 5, 6, 11, 12, 16, 17, 27, 28, 30, 31, 34 35, 36 and 38-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Budker (1998, Gene Therapy, Vol. 5, pg 272-276) in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203).

Budker taught administering naked plasmid DNA encoding marker protein into an artery in the leg of a rat, wherein pressure was applied to the artery using microvessel clips. Administration resulted in marker protein expression in all muscle groups of the leg (pg 274, col. 2, 1st full para.). The limitation of applying "transient" immunosuppression (step c; claim 41) is equivalent to temporarily occluding the blood vessels; the process of occluding blood vessels is "immunosuppression" because blood cells are prevented from flowing through that area. The limitation of applying "continuous" immunosuppression (claim 1, step c; claim 40) is taught by Milas because occlusion continues throughout the operation. The metes and bounds of "continuous" and "transient" immunosuppression are unclear (see 112/2nd). Budker also taught

injecting collagenase is also equivalent to "applying immunosuppression" because it disrupts the capillary membranes thereby decreasing the flow of blood through the immune system which is equivalent to "immunosuppression." Budker did not teach applying pressure to the mammal's limb epidermis as claimed.

However, Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the epidermis of the leg (pg 2198, Fig. 1A, see tourniquet on rat).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into an artery in the leg of a rat using pressure to deliver the DNA to all the muscle groups of the leg as taught by Budker wherein the plasmid was administered to the femoral artery and pressure was applied using a tourniquet applied to the epidermis of the leg as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using microvessel clips with using a tourniquet to reduce damage to the blood vessel and to eliminate time in surgery spent applying microvessel clips.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

7. Claims 1-3, 5, 6, 11, 12, 16, 17, 24, 25, 27-31, 34-36 and 38-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) in view of Nabel (US Patent 5,910,488, June 8, 1999).

Milas taught adenoviral particles to a femoral artery of a rat that was occluded using a tourniquet applied to the epidermis of the leg (pg 2198, Fig. 1A, see tourniquet on rat). The adenovirus was inherently delivered to skeletal muscle cells as claimed because the method of Milas is identical to that used by applicants in Example 10 (pg 32). Milas taught LacZ was expressed in tumor cells which is equivalent to "expression at detectable levels" as claimed. Milas did not teach using "immunosuppression" or naked DNA.

However, Nabel taught pre-treating with cytoxan (an immunosuppressant), and injecting naked plasmid DNA into an occluded blood vessel (col. 25, Example 14, lines 38-67; claim 20, col. 15, line 23). The limitation of "applying immunosuppression" is equivalent to pre-treating with cytoxan which eliminated suppressive T-cells. The pre-treating with cytoxan is "transient" immunosuppression (step c; claim 41) because the T-cells may return and "continuous" immunosuppression (claim 1, step c; claim 40) because the suppressive T-cells are eliminated throughout the operation.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer DNA into an artery using a tourniquet as taught by Milas wherein the artery was pre-treated using cytoxan as taught by Nabel. One of ordinary skill in the art at the time the invention was made would have been motivated to pre-treat the blood vessel of Milas with cytoxan to eliminate suppressive T-cells. One of ordinary skill in the art at the time the invention was made would have been motivated to use the method of Nabel using the tourniquet of Milas to eliminate steps in surgery. One of ordinary skill in the art at the time the

invention was made would have been motivated to use the method of Nabel to deliver DNA to muscle tissue to treat tumors in/adjacent to muscle tissue.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

8. Claims 1-3, 5, 6, 11, 12, 16, 17, 24, 25, 27-31, 34-36 and 38-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (US Patent 6,265,387, July 24, 2001) in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203).

Wolff taught delivering naked plasmid DNA to a clamped femoral artery and obtaining expression in the liver (col. 17, Example 8). Some of the animals received subcutaneous administration of dexamethasone the day before surgery (col. 18, line 45). The method of Wolff inherently resulted in delivery to skeletal muscle as claimed because the method requires increased pressure in the blood vessel as a result of the clamps and the delivery of the DNA within a short amount of time. Wolff did not teach using a tourniquet.

However, Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the epidermis of the leg (pg 2198, Fig. 1A, see tourniquet on rat).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into an artery in the leg of a rat using pressure to deliver the DNA to all the muscle groups of the leg as taught by Wolff using a tourniquet applied to the epidermis of the leg as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using

clamps of Wolff with using the tourniquet of Milas to reduce damage to the blood vessel and to eliminate time in surgury spent applying microvessel clips. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the adenoviral vector of Milas with the plasmid DNA of Wolff to prevent viral infection and to integrate the DNA into the genome.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. The rejection below is new based on the amendments to the claims.

Claims 1-3, 5, 6, 11, 12, 16, 17, 24, 25, 27-31, 34-36 and 38-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,265,387 in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203).

Wolff claimed delivering naked plasmid DNA to a bile duct, increasing the permeability of the bile duct and obtaining delivery and expression in the liver. Wolff did not claim delivering DNA to skeletal muscle as claimed.

However, Wolff taught clamps were used to increase permeability and taught delivering naked plasmid DNA to a clamped femoral artery and obtaining expression in the liver (col. 17, Example 8). Some of the animals recieved subcutaneous adminstration of dexamethasone the day before surgery (col. 18, line 45). The method of Wolff inherently resulted in delivery to skeletal muscle as claimed because the method requires increased pressure in the blood vessel as a result of the clamps and the delivery of the DNA within a short amount of time.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into a vessel, increasing permeability and obtaining expression as claimed by Wolff wherein the vessel was a

femoral artery, the permeability was increased using clamps and the DNA was delivered to skeletal muscle as taught in the specification of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated to inject the femoral artery instead of the bile duct as suggested in the specification of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated to use clamps to increase permeability in light of the disclosure of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated to deliver DNA to skeletal muscle instead of the liver as suggested in the disclosure of Wolff. The combined teachings of the claim and disclosure of Wolff did not teach using a tourniquet.

Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the epidermis of the leg (pg 2198, Fig. 1A, see tourniquet on rat).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into an artery in the leg of a rat using pressure to deliver the DNA to all the muscle groups of the leg as taught by the combined teachings of the claim and disclosure of Wolff using a tourniquet applied to the epidermis of the leg as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using clamps with using the tourniquet to reduce damage to the blood vessel and to eliminate time in surgery spent applying microvessel clips. One of ordinary skill in the art at the time the invention was made would have been

motivated to replace the adenoviral vector of Milas with naked plasmid DNA to prevent viral infection and to integrate the DNA into the genome.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER